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(Signature of person mailing)
E. Victor Donahue

(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Tonia Sue Agin, et al.

APPLICATION NO.: 10/578,162 : Examiner: Graser, Jennifer E.

FILING DATE: May 4, 2006 : Group Art Unit: 1645

TITLE: In Ovo Vaccination of Campylobacter In Avian Species :

Commissioner for Patents
Mailstop Amendment
P.O. Box 1450
Alexandria, VA. 22313-1450

Sir:

Reply to Non-Final Official Action

The present Reply is provided in response the non-final Official Action herein of January 16, 2009, whereinby all of the pending claims (Nos. 1-20) stand rejected. Reconsideration is respectfully requested in view of the following remarks.

The present invention is directed to the discovery that an effective and safe immune response against *Campylobacter* can be raised in birds, in ovo, by administration of live Campylobacter cells as immunogen. It has also been surprisingly discovered that such vaccination is safe, and does not harm the developing bird. Applicant respectfully believes that this invention is neither present in the prior art, nor is it suggested by any combination of teachings found in the prior art.

The section 102 rejection.

In the general practice of the avian vaccination art, it is generally recognized that direct vaccination into an egg with live bacteria is harmful to the developing embryo and may cause significant mortality. For example, live *Salmonella* and *E.coli* administered into a live egg are known to cause morbidity and mortality. The vaccinating microorganisms may end up in various tissues of the egg, and being opportunistic, may trigger infections against which the developing embryo is not able to properly – and quickly –defend against. This is hardly surprising, since even though such vaccines may present the host animal with

an overall excellent array of immunizing antigens, the pathogen is nonetheless live. Obviously, direct injection of live pathogens into the blood of mammals is similarly not recommended.

Although the Examiner has cited *Thoma et al.* (US 6,440,408) as anticipatory, in fact this reference sets the stage for the present invention. According to the clear teachings of this reference, live bacterial vaccines are unsafe, and should not be administered to eggs. Therefore, according to the teachings of this invention (see claim 18 thereof, and all throughout the specification), the vaccine consists of live bacterial cells which are invariably conjugated to neutralizing factors such as neutralizing antibodies and neutralizing antibody fragments. Administration of live bacterial cells without such neutralizing factors is not disclosed in the '408 patent, and the entire thrust of the specification is to teach fully away from the practicality and operability of the present invention. Finally, although the'408 specification contains numerous working examples, none are actually directed to *Campylobacter*.

Should the Examiner take the view that the "live cells" as mentioned in presently pending claim 1 are grammatically permitted to "comprise" an additional antibody components, i.e. that a live bacterium-antibody conjugate is nonetheless still a live bacterium, then Applicant's response is as follows. Irrespective of whether the live cells can generally comprise other components according to the meaning of the present invention, the compositions recited in the '408 patent are a *completely different invention*, as the invention of the '408 patent was clearly deemed by those authors to be essentially inoperable, in a practical sense, without added antibody. Accordingly, the Examiner is invited to contact the undersigned to agree upon specific claim language that sets aside any accidental grammatical overlap with the invention of the '408 patent, without unduly limiting the scope of the present invention.

The Section 103 rejections

In discussing the references that have been cited in support of rejections that have been made under 35 USC section 103, attention may first be directed to the newly cited article by G.C. Mead (attached via the Supplemental Information Disclosure Statement submitted herewith, and which reflects the thinking of those skilled in the art as of June 2002). The *Mead* article points to additional factors recognized in the art, that additionally teach away from the present invention. Not only are live bacterial vaccines generally known to be unsafe for administration to avian eggs (as the '408 patent clearly teaches), but

Campylobacter species possess unusual growth and behavior characteristics.

Campylobacter are best characterized as microaerophiles that live in the mucosa of the intestine. As explained by Mead (see the Abstract, for example), *Campylobacter* rarely cause disease in poultry, and they are carried asymptomatically in the alimentary tract of affected birds. Successful colonization of the intestinal villi may also involve numerous other environmental factors, and host interactions, which are not well understood. There is, however, considerable evidence that *Campylobacter* infection in poultry can lead to human enteritis, and therefore preventing the spread of the bacterium in farm poultry is of great importance. Although there are numerous approaches to providing bird flocks which are "Campylobacter-safe" (see Mead at 173) such as pre-colonizing the intestine with other competing bacterial species, there remains the clear problem that avian species are not to be *obviously* expected to mount vigorous immune responses against a microorganism that apparently causes them no harm., and even if an "immune response" is detected, is it of a kind that provides any practical effect and benefit. Further, if such immunization is to be accomplished, the question is how. As a result, it will be seen that there is no combination of the references cited under 35 USC section 103 that credibly predicts that the present invention would be successful.

The Examiner has rejected Claims 1-4, 6-8, and 13-15 under section 103 under a combination of *Noor et al.* and *Ziprin et al.* The rejection is respectfully traversed. Simply stated, there is nothing to combine, since, as the Examiner also notes, *Noor et al.* does not disclose live vaccines, and *Ziprin et al.* only discloses colonization experiments with live strains (including to elucidate the effects of mutations), with the intent of finding methods to prevent colonization, which is not obviously the same as causing and quantifying any effective immune that may be detected.

More specifically, *Ziprin et al.* is directed to the role of some *Campylobacter jenuni* genes on cecal colonization , and liver invasion. *Ziprin et al.* also discloses the in ovo delivery of certain *C. jejuni* strains, and strains containing mutations, to chicken embryos. The subsequent effect on cecal colonization and liver invasion in 14-day old in ovo-challenged birds was also measured. No information can be found in this reference that teaches that in ovo delivery of a live strain of *Campylobacter* induces an immune response which provides some degree of protection against colonization. In fact, the reference teaches that the in ovo challenge route using live cells of Campylobacter can lead to persistently infected birds.

Again referring to Mead (see at Page 171, first full paragraph, line 3), "although infection is associated with the production of specific immunoglobin (Cawthraw et al. 1994), these appear to have little or no effect on levels of intestinal carriage or the susceptibility to infection." Therefore, it is difficult to imagine that those skilled in the art would have concluded or even expected that the in ovo route would induce an immune response to infection, that is medically beneficial to human consumers, by actually protecting against intestinal colonization by *Campylobacter* in poultry. Indeed, Example 6 of the present specification is the first proof that reasonable success is possible, in regard of protecting against *Campylobacter* via live *in ovo* delivery. The totality of the references does not therefore support a *prima facie* rejection, especially in regard of a large scale and dependable process which is safe for the immunized birds.

Applicant respectfully believes that it is not necessary to address the remaining rejections, which the Examiner will recognize are only directed to specific and straightforward features in certain dependent claims.

Conclusion

An early and favorable action is respectfully requested. A Petition for Extension of Time (in duplicate) is enclosed.

Respectfully submitted,

Date: July 16, 2009

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